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(21) International Application Number: PCT/AU98/00906 (22) International Filing Date: 30 October 1998 (30.10.98) (30) Priority Data: PP 0103 30 October 1997 (30.10.97) AU (71) Applicant (for all designated States except US): VAYSMAN, Pyotr [AU/AU]; Tower 1, Suite 1107, Bondi Junction Plaza, 500 Oxford Street, Bondi Junction, NSW 2022 (AU). (71)(72) Applicant and Inventor: VAISMAN, Jakov [AU/AU]; Tower 1, Suite 1107, Bondi Junction Plaza, 500 Oxford Street, Bondi Junction, NSW 2022 (AU). (74) Agent: WATERMARK PATENT & TRADEMARK ATTORNEYS; Unit 1, The Village, Riverside Corporate Park, 39-117 Delhi Road, North Ryde, NSW 2113 (AU).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: METHOD AND COMPOSITION FOR TREATMENT OF SEXUAL DYSFUNCTION		
(57) Abstract Disclosed is a composition and method of treatment for sexual dysfunction, in both male and female mammals. The composition is preferably a combination of a relatively low dose of milrinone, in combination with one or more of an alpha-adrenergic blocker, a phosphodiesterase inhibitor, a PGE prostaglandin type, or an atropinic agent. The composition is preferably administered via intracavernosal injection, or for females via a topical composition.		

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Method and Composition for Treatment of Sexual Dysfunction

Technical Field

The present invention relates to the treatment of erectogenic dysfunction in males, and to the treatment of anorgasmia in women.

5 Background Art

It has been known to treat erectogenic dysfunction in men using so-called self injection therapy, following from the work of Virag - for example, see R Virag et al, *Intercavernous Injection of Papaverine as a Diagnostic and Therapeutic Method in Erectile Failure*, *Angiologyn* ,35, pp 79-87 (1984). Various
10 compounds have been used in this treatment technique. For example, in US patent No. 5474535 to Place et al, there is a disclosure of a large group of therapeutic agents suitable for use in the treatment of impotence, with a preferred composition being a combination of alpha blockers and prostaglandin. Various agents and combinations have been described in the literature.
15 However, the improvement of the treatment regimes and the compositions used has been largely a matter of trial and error. Whilst many patients can be helped with existing treatments, there is a minority who do not achieve erection using existing drug therapies. There is still no well understood theoretical regime which can predict the likely effectiveness or otherwise of any particular
20 compound or combination of compounds, and hence it is not possible to predict whether a given combination will be more or less efficacious than the components given alone.

In an abstract by Stief et al, published in *International Journal of Impotence Research, Basic and Clinical Studies*, Stockton, v. 8 No. 3,
25 September 1996, p. 127, Abstract D20 , trials are disclosed in which Milrinone was tested for its effects on samples of tissue from human and rabbit corpus cavernosum. In vivo trials were also conducted, and erectile response was reported in humans from treatment with Milrinone alone.

In an abstract by Sparwasser et al, also published in *International*
30 *Journal of Impotence Research, Basic and Clinical Studies*, Stockton, v. 8 No. 3, September 1996, p. 127, Abstract D22, trials were conducted using cavernosal tissue to determine the efficacy of various PDE inhibitors, including

Milrinone. The abstract suggests that on the basis of the tissue trials Milrinone may be an effective treatment for erectogenic dysfunction.

Milrinone is a type III PDE inhibitor, which functions as a positive inotrope and vasodilator in its conventional clinical use, but has various adverse
5 reactions. These include ventricular arrhythmias, ventricular extopic activity, ventricular tachycardia, and ventricular fibrillation. It is accordingly not desirable administer large doses, particularly when many patients are middle aged and older men who may well be susceptible to cardiovascular or circulatory disorders.

10 Trials by the inventor have indicated that Milrinone is not effective as an erectogenic agent when administered alone at safe doses. Milrinone is a powerful vasoactive substance, and administration of substantial doses by, for example, penile injection carries a risk of deleteriously effecting the circulatory system as a whole.

15 It is one object of the present invention to provide a composition including milrinone which is as or more effective than existing compositions in the treatment of impotence. It is a further object of the present invention to provide an improved method of treatment for impotence.

It is postulated by the inventor that one cause of female anorgasmia is the
20 inability of some women to achieve rigidity of the clitoris during sexual activity, and that accordingly similar pharmacological agents and compositions, suitably reformulated for topical use, may be effective in the treatment of female anorgasmia. Accordingly, another object of the present invention is to provide a new composition and method of treatment for female anorgasmia.

25 **Summary of the Invention**

The present invention provides in one aspect a composition for use in the treatment of sexual dysfunction, comprising an effective amount of milrinone, a pharmaceutically acceptable carrier or diluent, and one or more agents selected from the group comprising an alpha-adrenergic blocker, a phosphodiesterase
30 inhibitor, a PGE prostaglandin type E, an atropinic agent, with the alpha blocker itself being composed of one part alpha 1 and one part alpha 2.

According to one other aspect, the present invention comprises a method

of treating sexual dysfunction in a mammal, which comprises administering to said mammal a effective amount of a composition comprising in combination Milrinone, and one or more therapeutically active agents selected from the group comprising an alpha-adrenergic blocker composed of one part alpha 1
5 and one part alpha 2, a phosphodiesterase inhibitor, a PGE type prostaglandin, and an atropinic agent.

Preferably, the composition is administered by intracavernous injection, topical, transdermal, or intraurethrally.

According to another aspect the present invention comprises the use of
10 milrinone in the manufacture of a medicament for the treatment of sexual dysfunction, said medicament comprising an effective amount of milrinone and a pharmaceutically acceptable carrier or diluent.

Preferably, the medicament further comprises one or more further therapeutic agents which either facilitate, potentiate or are erectogenic. Most
15 preferably the additional therapeutic agents are selected from the group comprising an alpha-adrenergic blocker composed of one part alpha 1 and one part alpha 2, a phosphodiesterase inhibitor, a PGE prostaglandin type, and an atropinic agent .

It has been discovered by the inventor that when Milrinone is
20 administered in combination with other erectogenic agents, a strong synergistic effect occurs, to the extent that these combinations are more effective than combinations previously used, and much more effective than the components when given alone. Some patients who did not achieve erection using conventional therapies achieved erection using the inventive therapy.

25 **Description**

The present invention will be described and exemplified in relation to several particular compositions and comparative trials as set out below. It is emphasised, however, that the precise dosage and treatment regime will be determined by the attending physician, depending upon the particular
30 circumstances of each patient - for example age, response to particular medications, general health and cardiovascular condition. Hence, the precise dosages and elements of the therapeutic compositions will vary in any true clinical situation.

In the trial set out below, the erectogenic activity of milrinone alone or in combination with papaverine, chlorpromazine, phentolamine, atropine, yohimbine and prostaglandin E1 was compared to that of combinations of papaverine, chlorpromazine, phentolamine, atropine, yohimbine and
5 prostaglandin E1.

These effects were studied in 176 patients with multiple pathogenic factors. The grade of erection was determined by palpation and inspection of the penis by the same doctor in all patients, according to a scale from one to five (one (1) - no erection, two (2) - slight tumescence, three (3) - full tumescence
10 without rigidity, four (4) - incomplete rigidity and five (5) - full rigidity). The latent period between injection and erection, duration of the erection and side effects were also recorded.

Arterial blood flow was evaluated by Doppler ultrasound and an average flow velocity of 20-25 cm per second was assumed as the lower limit of normal.

15 **STUDY RESULTS**

Milrinone Only:

After the injection of milrinone 1 mg. alone into 12 patients, 5 (41%) showed no response or slight tumescence only (grades 1 to 2), 4 (33%) had tumescence without rigidity (grade 3) and the other 3 (25%) achieved erections
20 with rigidity of grades 4 to 5 and the other. The mean latency time between injection and erection was 12 minutes and the mean duration of erection was 28 minutes.

Atropine only:

After the injection of atropine 0.12 mg. into 9 patients, all 9 showed no
25 response (grades 1).

Atropine vs Atropine Milrinone:

After the injection of atropine 0.12 mg. into 11 patients, all 11 showed no response (grades 1).

After the injection of milrinone 0.38 mg. and atropine 0.12 mg. into the
30 same 11 patients, 7 (64%) achieved erections with rigidity of grades 4 to 5 and the other 4 (36%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 10 minutes and the mean duration of erection was 43 minutes.

Chlorpromazine, Atropine versus Chlorpromazine, Atropine, Milrinone:

After the injection of chlorpromazine 3.1 mg. and atropine 0.12 mg. into 8 patients, all 8 showed no response (grades 1).

After the injection of milrinone 0.38 mg., chlorpromazine 3.1 mg. and atropine 0.12 mg. into the same 8 patients, 5 (62%) achieved erections with rigidity of grades 4 to 5 and the other 3 (38%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 11 minutes and the mean duration of erection was 39 minutes.

Phentolamine, Atropine versus Phentolamine, Atropine, Milrinone:

After the injection of phentolamine 2 mg. and atropine 0.2 mg. into 9 patients, all 9 showed no response (grades 1).

After the injection of milrinone 0.38 mg., phentolamine 2 mg. and atropine 0.2 mg. into the same 9 patients, 6 (67%) achieved erections with rigidity of grades 4 to 5 and the other 3 (33%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 8 minutes and the mean duration of erection was 58 minutes.

Papaverine, Chlorpromazine, Atropine versus Papaverine, Chlorpromazine, Atropine, Milrinone:

After the injection of papaverine 11.25 mg., chlorpromazine 3.1 mg. and atropine 0.12 mg. into 13 patients, 7 (54%) achieved erections with rigidity of grades 4 to 5 and the other 6 (46%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 9 minutes and the mean duration of erection was 78 minutes.

After the injection of milrinone 0.38 mg., papaverine 11.25 mg., chlorpromazine 3.1 mg. and atropine 0.12 mg. into the same 13 patients, 11 (84%) achieved erections with rigidity of grades 4 to 5 and the other 2 (16%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 9 minutes and the mean duration of erection was 96 minutes.

Papaverine, Phentolamine, Atropine versus Papaverine, Phentolamine, Atropine, Milrinone:

After the injection of papaverine 11.25 mg., phentolamine 2 mg. and atropine 0.2 mg. into 14 patients, 8 (57%) achieved erections with rigidity of grades 4 to 5 and the other 6 (43%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 8 minutes and the mean duration of erection was 98 minutes.

After the injection of milrinone 0.38 mg., papaverine 11.25 mg., phentolamine 2 mg. and atropine 0.2 mg. into the same 14 patients, 12 (85%) achieved erections with rigidity of grades 4 to 5 and the other 2 (15%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 7 minutes and the mean duration of erection was 126 minutes.

Papaverine. Chlorpromazine. Atropine. Yohimbine versus Papaverine. Chlorpromazine. Atropine. Yohimbine. Milrinone:

After the injection of papaverine 15 mg., chlorpromazine 5 mg., atropine 0.15 mg. and yohimbine 1.75 mg. into 50 patients, 35 (70%) achieved erections with rigidity of grades 4 to 5 and the other 15 (30%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 9 minutes and the mean duration of erection was 86 minutes.

After the injection of milrinone 0.38 mg., papaverine 15 mg., chlorpromazine 5 mg., atropine 0.15 mg. and yohimbine 1.75 mg. into the same 50 patients, 48 (96%) achieved erections with rigidity of grades 4 to 5 and the other 2 (4%) had tumescence without rigidity (grade 3). The mean latency time between injection was 9 minutes and the mean duration of erection was 138 minutes.

Papaverine. Phentolamine. Atropine. Yohimbine versus Papaverine. Phentolamine. Atropine. Yohimbine. Milrinone:

After the injection of papaverine 15 mg., phentolamine 2 mg., atropine 0.15 mg. and yohimbine 1.75 mg. into 18 patients, 13 (72%) achieved erections with rigidity of grades 4 to 5 and the other 5 (28%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 10 minutes and the mean duration of erection was 73 minutes.

After the injection of milrinone 0.38 mg., papaverine 15 mg., phentolamine 2 mg., atropine 0.15 mg. and yohimbine 1.75 mg. into the same

18 patients, 17 (94%) achieved erections with rigidity of grades 4 to 5 and the other 1 (6%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 8 minutes and the mean duration of erection was 124 minutes.

5 Papaverine, Chlorpromazine, Atropine, Prostaglandin E1 versus Papaverine, Chlorpromazine, Atropine, Prostaglandin E1, Milrinone:

After the injection of papaverine 11.25 mg., chlorpromazine 3.1 mg., atropine 0.12 mg. and prostaglandin E1 5 mcg. into 9 patients, 6 (67%) achieved erections with rigidity of grades 4 to 5 and the other 3 (33%) had
10 tumescence without rigidity (grade 3). The mean latency time between injection and erection was 10 minutes and the mean duration of erection was 92 minutes.

After the injection of milrinone 0.38 mg., papaverine 11.25 mg., chlorpromazine 3.1 mg., atropine 0.12 mg. and prostaglandin E1 5 mcg. into the same 9 patients, 8 (89%) achieved erections with rigidity of grades 4 to 5 and
15 the other 1 (11%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 9 minutes and the mean duration of erection was 134 minutes.

Papaverine, Phentolamine, Atropine, Prostaglandin E1 versus Papaverine, Phentolamine, Atropine, Prostaglandin E1, Milrinone:

20 After the injection of papaverine 18 mg., phentolamine 2 mg., atropine 0.2 mg. and prostaglandin E1 5 mcg. into 14 patients, 10 (71%) achieved erections with rigidity of grades 4 to 5 and the other 4 (29%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 11 minutes and the mean duration of erection was 82 minutes.

25 After the injection of milrinone 0.38 mg., papaverine 18 mg., phentolamine 2 mg., atropine 0.2 mg. and prostaglandin E1 5 mcg. into the same 14 patients, 13 (82%) achieved erections with rigidity of grades 4 to 5 and the other 1 (8%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 9 minutes and the mean duration of
30 erection was 143 minutes.

Papaverine, Chlorpromazine, Atropine, Yohimbine, Prostaglandin E1 versus Papaverine, Chlorpromazine, Atropine, Yohimbine, Prostaglandin E1, Milrinone:

After the injection of papaverine 15 mg., chlorpromazine 5 mg., atropine 0.15 mg., yohimbine 1.75 mg. and prostaglandin E1 5 mcg. into 18 patients, 14 (78%) achieved erections with rigidity of grades 4 to 5 and the other 4 (22%) had tumescence without rigidity (grade 3). The mean latency time between
5 injection and erection was 11 minutes and the mean duration of erection was 76 minutes.

After the injection of milrinone 0.38 mg., papaverine 15 mg., chlorpromazine 5 mg., atropine 0.15 mg., yohimbine 1.75 mg. and prostaglandin E1 5 mcg. into the same 18 patients, 17 (94%) achieved erections with rigidity of grades 4 to 5 and the other 1 (6%) had tumescence without rigidity (grade 3).

- 5 The mean latency time between injection and erection was 10 minutes and the mean duration of erection was 143 minutes.

Papaverine, Phentolamine, Atropine, Yohimbine, Prostaglandin E1 versus Papaverine, Phentolamine, Atropine, Yohimbine, Prostaglandin E1, Milrinone:

- After the injection of papaverine 18 mg., phentolamine 2 mg., atropine 0.2 mg., yohimbine 1.75 mg. and prostaglandin E1 5 mcg. into 11 patients, 8 (73%) achieved erections with rigidity of grades 4 to 5 and the other 3 (27%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 8 minutes and the mean duration of erection was 84 minutes.

- After the injection of milrinone 0.38 mg. papaverine 18 mg., phentolamine 2 mg., atropine 0.2 mg., yohimbine 1.75 mg. and prostaglandin E1 5 mcg. into the same 11 patients, 10 (91%) achieved erections with rigidity of grades 4 to 5 and the other 1 (9%) had tumescence without rigidity (grade 3). The mean latency time between injection and erection was 8 minutes and the mean duration of erection was 132 minutes.

20 **Summary of study results**

- Milrinone alone produced erectogenic activity markedly lower than due to any combination of papaverine, chlorpromazine, phentolamine, atropine, yohimbine and prostaglandin E1, both in terms of the rigidity and duration of responses. However, when combined with papaverine, chlorpromazine, phentolamine, atropine, yohimbine and prostaglandin E1, milrinone proved to evoke erections similar to erections experienced by the patients during normal sexual intercourse. It is postulated that the combination of different mechanisms of action is a possible explanation for such a strong synergistic behaviour with milrinone.

- 30 Together with papaverine and even more potent than papaverine, milrinone acts on a post-receptor level via the inhibition of phosphodiesterase (the consequent increase in cyclic adenosine monophosphate attenuates the

α 1 (alpha 1) receptor-mediated contraction of the smooth muscle cell, possibly by interfering with the calcium ion-mobilisation). Furthermore, the alpha blocking properties of yohimbine seem to be at least as effective as phentolamine if not more so, whereas prostaglandin E1 acts via a membrane-
5 receptor. Atropine works by potentiating the action of the other active products on pathological erectile tissue by interfering with the mechanisms that trigger the relaxation of smooth muscle, especially the EDRF (Endothelium Releasing Factor).

It is concluded that a combination of milrinone with any combination of
10 papaverine, chlorpromazine, phentolamine, atropine, yohimbine and prostaglandin E1 is significantly more effective than any combination of papaverine, chlorpromazine, phentolamine, atropine, yohimbine and prostaglandin E1 without milrinone.

Accordingly, it is believed that a strong synergistic effect has been
15 demonstrated, so that milrinone included at a relatively low dose in a composition for the treatment of impotence enhances the effectiveness of the composition in a way which does not correlate with the activity of Milrinone alone or with the activity of the other components of the composition even when these other components are used in combination..

20 A further advantage of the present invention is that it allows prostaglandin E1 to be omitted from the therapeutic combination. For some patients, prostaglandin E1 produces significant side effects (pain at the site of the injection) while other patients have only a weak response to weak response to prostaglandin E1 (due to a low receptor density).

25 It will be understood that analogues to the components described above may exhibit similar clinical activity to those particularly discussed, and that the present invention is not limited to the specific compounds discussed above in combination with Milrinone.

Effects of Clitoral Application of Milrinone Gel in Combination with Papaverine,
30 Chlorpromazine, Phentolamine, Atropine and Yohimbine in Women with
Orgasmic Dysfunction

Clitoral Doppler ultrasonography was studied in 8 heterosexual active female volunteers with primary anorgasmia. Significant changes from baseline of all Doppler parameters was found before and after clitoral application of milrinone gel. The results obtained in this study showed a striking similarity
5 between female clitoral vascular response and male cavernosal vascular response after intracavernosal injection of milrinone in combination with papaverine, chlorpromazine, phentolamine, atropine and yohimbine. After clitoral application of milrinone gel during the sexual excitement phase, all 8 women for the first time achieved full orgasm through intercourse or even during
10 manual stimulation by the partner.

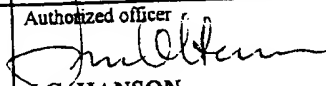
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating sexual dysfunction in mammals, which comprises of administering to said mammal an effective amount of milrinone.
2. The method according to claim 1 wherein the milrinone is used in combination with one or more therapeutically active agents selected from an alpha-adrenergic blocker, a phosphodiesterase inhibitor, a PGE prostaglandin type, an atropinic agent, with the alpha blocker itself being composed of one part alpha 1 and one part alpha 2.
3. The method according to claim 1 and 2, wherein the method of treating is by intracavernous injection, topical, transdermal, or intraurethral administration of the milrinone.
4. The use of milrinone in the manufacture of a medicament for the treatment of sexual dysfunction comprising an effective amount of milrinone and a pharmaceutically acceptable carrier or diluent.
5. The use according to claim 4 which further comprises one or more additional therapeutic agents which either facilitate, potentiate or are erectogenic.
6. The use according to claim 3 wherein the additional agents comprise one or more agents selected from the group comprising an alpha-adrenergic blocker, a phosphodiesterase inhibitor, a PGE prostaglandin type E, an atropinic agent, with the alpha blocker itself being composed of one part alpha 1 and one part alpha 2.

7. The use according to claim 6 wherein the composition is formulated so as to be administered by intracavernous injection, topically, transdermally, or intraurethrally.
8. The use according to claims 4 to 7 wherein the composition further comprises a penetration-enhancing agent.
9. A composition for use in the treatment of sexual dysfunction, comprising an effective amount of milrinone, a pharmaceutically acceptable carrier or diluent, and one or more agents selected from the group comprising an alpha-adrenergic blocker, a phosphodiesterase inhibitor, a PGE prostaglandin type E, an atropinic agent, with the alpha blocker itself being composed of one part alpha 1 and one part alpha 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00906

A. CLASSIFICATION OF SUBJECT MATTER		
Int Cl ⁶ : A61K 31/44		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61K with electronic database search terms as indicated below		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU: IPC AS ABOVE		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) DERWENT: (Milrinone or Corotrope or Primacor) MEDLINE: (Milrinone or Corotrope or Primacor) and (SEX? OR IMPOT? OR ANORG? and CAS: OR CLIT? OR ERECT? OR CAVERNOUS?)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 4338948 A (CARLEN, J) 18 May 1995 whole document	1, 3, 4, 8
X	Int. J. Impotence Res, Vol 8 No 3, September 1996, page 127 -abstract D20, "The effect of the specific Phosphodiesterase (PDE) - inhibitors on Human Rabbit Cavernous Tissue in vitro and in vivo', Stief et al	1, 3, 4
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
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Date of the actual completion of the international search 17 December 1998		Date of mailing of the international search report 05 January 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer  J.G. HANSON Telephone No.: (02) 6283 2262

INTERNATIONAL SEARCH REPORT

International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	-Abstract D22 "The effects of inhibitors of Phosphodiesterase (PDE) on Smooth Muscle Relaxation of Human and Rabbit Isolated Cavernosal Tissue", Spanwasser et al	1, 3, 4
P,X	J. Urology, Vol 159 No 4 April 1998 pages 1390-1393 "The Effect of the Specific Phosphodiesterase (PDE) inhibitors on Human and Rabbit Cavernous Tissue in vitro and in vivo", Stief et al	1, 3, 4
Y	see abstract, page 1391, fig 5, 1393	2, 5, 6, 9
Y	US-A- 5583144 Kral, 10 December 1996 col 1 lines 51-62, col 4 lines 31-43, Example 1, 2	1-9
Y	WO 95/05172 A (Zonagen Inc) 23 February 1995 page 5 lines 27 - page 6 line 16, page 7 lines 1-5, page 10 line 18 - page 11 line 11	1-9
Y	The Merck Index, 12 Edn 1996, Merck & Co Mon. No 6284, 1036, 7417, 2238, 8063, 8064, 7151, 907	1-9
A	Annales d'urologie, Vol 25 No 2 (1991) pages 64-66 "Pathophysiology of erectile dysfunction due to cavernous venous insufficiency", Stief, C.G.	

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International application No.
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This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
US	5583144	WO	98/09627	AU	69711/96		
WO	95/05172	BR	9407250	CA	2169071	CN	1128950
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